Clinical Pharmacology during Pregnancy:
Efforts of the MFMU and OPRU to expand understanding

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UTMB-Galveston
No conflicts of interest

Support

- 2 U54 HD047891
- 1 R01 HD083003
Objectives

- Issues associated with medications use in pregnancy
- Pregnancy special considerations
- Experience from NICHD MFMU/OPRC networks
Medications Use During Pregnancy

Mitchell A. et al AJOG 2011
Medications use during pregnancy: Maternal Age

Mitchell A. et al AJOG 2011
Exposure to Antihypertensive Medications in Pregnancy

Antidepressants use during pregnancy

Mitchell A. et al AJOG 2011
Medications use during pregnancy

Mitchell A. et al AJOG 2011
First Trimester

- Critical period for organogenesis

- Many women unaware of their pregnancy
Teratogenicity, while important, is not the only safety concern.
Other Concerns in Pregnancy: Dosing

- Lack of data on dosage
- Vast majority of efficacy/safety studies done without knowledge of PK/PD
Proportions of PK trials in pregnancy

McComack & Best. Frontiers 2014
Proportions of PK trials in pregnancy
Exclusion of Pregnant Women: Protocols reviewed by an IRB over 1 year

<table>
<thead>
<tr>
<th></th>
<th>Exclude pregnant women</th>
<th>Require Pregnancy Testing</th>
<th>Require Contraception</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Protocols</strong> (n=71)</td>
<td>53 (75%)</td>
<td>40 (56%)</td>
<td>42 (59%)</td>
</tr>
<tr>
<td><strong>All drug studies</strong> (n=52)</td>
<td>48 (92%)</td>
<td>37 (71%)</td>
<td>41 (79%)</td>
</tr>
<tr>
<td><strong>IND drug studies</strong> (n=38)</td>
<td>35 (92%)</td>
<td>31 (82%)</td>
<td>34 (89%)</td>
</tr>
<tr>
<td><strong>Non-IND drug studies</strong> (n=14)</td>
<td>13 (93%)</td>
<td>6 (43%)</td>
<td>7 (50%)</td>
</tr>
</tbody>
</table>

Schonfeld T, et.al. IRB 2013
Concerns for medications use in pregnancy

- Lack of data on dosage
  - Physicians extrapolate drug dosage regimens from non-pregnant subjects or men
- Can lead to under or overdosing
  - Efficacy and toxicity might be affected
Pregnancy changes
Pharmacokinetics
“What the body does to the drug”

ADME
- Absorption
- Distribution
- Metabolism
- Elimination

Pharmacodynamics
“What the drug does to the body”

Clinical relevance
- Efficacy
- Safety
Drug disposition during pregnancy: physiologic changes

- Absorption:
  - Delayed gastric emptying and decreases GI motility

- Elimination
  - Increased GFR

## Analysis of Weight Gain During Pregnancy

<table>
<thead>
<tr>
<th>Tissues and Fluids</th>
<th>10 weeks</th>
<th>20 weeks</th>
<th>30 weeks</th>
<th>40 weeks (Total)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fetus</strong></td>
<td>5</td>
<td>300</td>
<td>1500</td>
<td>3400</td>
</tr>
<tr>
<td><strong>Placenta</strong></td>
<td>20</td>
<td>170</td>
<td>30</td>
<td>650</td>
</tr>
<tr>
<td><strong>Amniotic fluid</strong></td>
<td>30</td>
<td>350</td>
<td>750</td>
<td>800</td>
</tr>
<tr>
<td><strong>Uterus</strong></td>
<td>140</td>
<td>320</td>
<td>600</td>
<td>970</td>
</tr>
<tr>
<td><strong>Breasts</strong></td>
<td>45</td>
<td>180</td>
<td>360</td>
<td>405</td>
</tr>
<tr>
<td><strong>Blood</strong></td>
<td>100</td>
<td>600</td>
<td>1300</td>
<td>1450</td>
</tr>
<tr>
<td><strong>Extravascular fluid</strong></td>
<td>0</td>
<td>30</td>
<td>80</td>
<td>1480</td>
</tr>
<tr>
<td><strong>Maternal stores (fat)</strong></td>
<td>310</td>
<td>2050</td>
<td>3480</td>
<td>3345</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>650</td>
<td>4000</td>
<td>8500</td>
<td>12,500</td>
</tr>
</tbody>
</table>

Chapter 8: Williams Obstetrics, 5th edition
Implications

- ↑ water --> larger volume of distribution of water soluble drugs
- ↑ fat --> larger volume of distribution for lipid soluble drugs

- ↓ maximal serum concentrations
  - Less effective
  - Higher dose to obtain therapeutic levels

Anger and Piquette-Miller, 2008
Dawes and Chowienczyk, 2001
# Changes in Metabolizing Enzymes Activity & Apparent oral clearance

<table>
<thead>
<tr>
<th>Drug/probe</th>
<th>Indication</th>
<th>Effect on CL/F (%)(^a)</th>
<th>Metabolizing-enzyme activity changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine(^*)</td>
<td>CNS stimulant</td>
<td>↓ 33</td>
<td>↓ CYP1A2</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Asthma</td>
<td>↔</td>
<td>↓ 34</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Smoking cessation</td>
<td>↑ 54</td>
<td>↑ CYP2A6</td>
</tr>
<tr>
<td>Phenytoin(^*,b)</td>
<td>Epilepsy</td>
<td>↑ 43</td>
<td>↑ CYP2C9</td>
</tr>
<tr>
<td>Proguanil</td>
<td>Malaria</td>
<td>↓ 60</td>
<td>↓ CYP2C19</td>
</tr>
<tr>
<td>Metoprolol(^*)</td>
<td>Hypertension</td>
<td>↑ 459</td>
<td>↑ CYP2D6</td>
</tr>
<tr>
<td>Dextromethorphan(^b)</td>
<td>Cough</td>
<td>↑ 26</td>
<td></td>
</tr>
<tr>
<td>Midazolam(^*)</td>
<td>Sedation</td>
<td>↑ 99</td>
<td>↑ CYP3A4</td>
</tr>
<tr>
<td>Indinavir</td>
<td>HIV infection</td>
<td>↑ 101</td>
<td>↑ CYP2B6</td>
</tr>
<tr>
<td>Glyburide</td>
<td>Diabetes</td>
<td>↑ 106</td>
<td>↑ UGT1A1</td>
</tr>
<tr>
<td>Methadone</td>
<td>Addiction</td>
<td>↑ 101</td>
<td>↑ 65</td>
</tr>
<tr>
<td>Labetalol</td>
<td>Hypertension</td>
<td>↑ 30</td>
<td>↑ 30</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Epilepsy</td>
<td>↑ 200</td>
<td>↑ 300</td>
</tr>
<tr>
<td>Zidovudine(^c)</td>
<td>HIV infection</td>
<td>↑ 200</td>
<td>↔ UGT2B7</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Bacterial infection</td>
<td>↑ 23</td>
<td>↑ 20</td>
</tr>
<tr>
<td>Metformin(^*)</td>
<td>Diabetes</td>
<td>↑ 22</td>
<td>↑ 11</td>
</tr>
<tr>
<td>Digoxin(^*)</td>
<td>Cardiac diseases</td>
<td>NA</td>
<td>↑ 19</td>
</tr>
</tbody>
</table>

Ke AB et al. Annu Rev Pharmacol toxicol 2014
Need Drug Research in Pregnancy and Lactation
Preeclampsia

- 5-7%

- 1/5 of all maternal death in the US

- 50,000/yr maternal death from eclampsia in the world
Complications in severe preeclampsia

**Maternal**
- Eclampsia
- CVA
- Uncontrolled hypertension
- Kidney injury
- Pulmonary edema
- Liver injury
- Death

**Fetal/neonatal**
- Stillbirth
- Abruption
- Growth restriction
- Premature delivery
- Long term adverse outcomes
Preeclampsia: a Cardiovascular Disease

- Overlapping pathophysiology & common risk factors
  - DM, HTN, Obesity, Dyslipidemia

- Common mechanisms
  - Inflammation
  - Endothelial dysfunction

- American Heart Association - 2011

Brends et al. Hypertension 2008
Hansson et al. NEJM 2005
Redman et al. Science 2005
Prevention

- **Preeclampsia prevention**
  - Ca, Vit C & E, fish oil
  - Low dose aspirin

- **Cardiovascular disease prevention**
  - HMG-CoA reductase inhibitors (statins)

Barton et al Obstet Gynecol 2008
Askie et al Lancet 2007
Brugts et al BMJ 2009
Mills et al J Am Coll Cardiol 2008
Statins for Preeclampsia Prevention
Murine Preeclampsia Model

sFlt-1 expression

- High BP
- Altered vascular profile
- Proteinuria
- Glomerular endotheliosis
- Placental hypoxia
- IUGR

Kumasawa et al. PNAS 2011
Maynard et al., JCI 2003
Lu et al., Am J Obstet Gynecol 2007
Pravastatin in Animal Models of Preeclampsia

• ↓ sFlt-1 & ↑ PlGF
• ↓ BP
• ↑ eNOS
• Improves vascular reactivity
• ↓ Proteinuria
• ↓ Oxidative stress
• Restores fetal growth

• No ↑ pup resorption
• No pup deformation

Kumasawa et al. PNAS 2010
Costantine et al., Obs Gyn 2010
Ahmed et al., PLoS ONE 2010
Singh et al, HTN 2011
Fox et al., AJOG 2011
Bauer et al, HTN 2013
Can We Use Statins in Pregnancy?
Class X

- Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.
Pravastatin: Pregnancy Experience

■ Animal data:
  ■ Not teratogenic (10-120x human exposure)
  ■ No effect on placental and pup weights

■ Human Cohorts:
  ■ No increased rate of congenital anomalies, SAB, IUFD.
  ■ No effect on fetal growth

Relative Lipophilicity of Statins

McTaggart, Am J Cardiol 2001
A Randomized Controlled Trial of Pravastatin for the Prevention of Preeclampsia in High Risk Women
VOTE

9 YES  7 NO
Transplacental transfer and distribution of pravastatin

Tatiana N. Nanovskaya, PhD; Svetlana L. Patrikeeva, MS; Jonathan Paul, PhD; Maged M. Costantine, MD; Gary D. V. Hankins, MD; Mahmoud S. Ahmed, PhD
Placental transfer studies: Clearance index

Placental transfer studies

**Fig. 1.** Mean pravastatin transfer with simulation to correct for protein binding and elimination half life.

Zarek et al, Placenta 2013
Pravastatin for the Prevention of Preeclampsia in High-Risk Women: A Pilot Study

Obstetric-Fetal Pharmacology Research Units (OPRU) Network
The National Institute of Child Health and Human Development
Primary Research Questions

- What are the Pharmacokinetic properties and maternal and fetal safety profiles of pravastatin when used as a prophylactic daily treatment in pregnant women at high risk of preeclampsia?

NCT01717586
OBSTETRICS

Safety and pharmacokinetics of pravastatin used for the prevention of preeclampsia in high-risk pregnant women: a pilot randomized controlled trial

Maged M. Costantine, MD; Kirsten Cleary, MD; Mary F. Hebert, PharmD, FCCP; Mahmoud S. Ahmed, PhD; Linda M. Brown, DrPH; Zhaoxia Ren, MD, PhD; Thomas R. Easterling, MD; David M. Haas, MD, MS; Laura S. Haneline, MD; Steve N. Caritis, MD; Raman Venkataramanan, PhD; Holly West, DHEd; Mary D’Alton, MD; Gary Hankins, MD; for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Obstetric-Fetal Pharmacology Research Units Network

ClinicalTrials.gov

NCT01717586
<table>
<thead>
<tr>
<th>Parameter</th>
<th>18–24 wks gestation (n = 11)</th>
<th>30–34 wks gestation (n = 10)</th>
<th>4–6 mo postpartum (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$, ng/mL</td>
<td>14.9 ± 11.3</td>
<td>11.1 ± 6.2</td>
<td>17.2 ± 11.5</td>
</tr>
<tr>
<td>$T_{\text{max}}$, h</td>
<td>1.6 ± 0.6</td>
<td>1.5 ± 0.4</td>
<td>1.6 ± 1.0</td>
</tr>
<tr>
<td>Half-life, h</td>
<td>2.1 ± 0.9</td>
<td>3.0 ± 1.6</td>
<td>2.4 ± 1.3</td>
</tr>
<tr>
<td>CL/F, L/h</td>
<td>396 ± 190</td>
<td>389 ± 215</td>
<td>289 ± 142</td>
</tr>
<tr>
<td>CL/F, L/h/kg</td>
<td>4.6 ± 2.4</td>
<td>4.2 ± 2.0</td>
<td>3.2 ± 1.5</td>
</tr>
<tr>
<td>AUC(0–24), ng/h/mL</td>
<td>31 ± 16</td>
<td>32 ± 16</td>
<td>43 ± 20</td>
</tr>
<tr>
<td>Amount excreted (0–24 h), mg</td>
<td>0.98 ± 0.60</td>
<td>1.04 ± 0.57</td>
<td>0.93 ± 0.60</td>
</tr>
<tr>
<td>Percent excreted unchanged</td>
<td>10 ± 6</td>
<td>10 ± 6</td>
<td>9 ± 6</td>
</tr>
<tr>
<td>$CL_{\text{renal}}$, L/h</td>
<td>$34 ± 16^a$</td>
<td>$34 ± 11^a$</td>
<td>$23 ± 4$</td>
</tr>
<tr>
<td>$CL_{\text{secretion}}$, mL/min</td>
<td>$480 ± 273^a$</td>
<td>$471 ± 151^a$</td>
<td>$325 ± 65$</td>
</tr>
</tbody>
</table>
A Randomized Controlled Trial of Pravastatin for the Prevention of Preeclampsia in High Risk Women
VOTE

15 YES  1 NO
Project Development Timeline

Pre-clinical work
Project Development Timeline
Project Development Timeline

Pre-clinical work -> MFMU -> OPRU
Project Development Timeline

Pre-clinical work → MFMU → OPRU → FDA IND → OPRU Pilot phase 1
Project Development Timeline

- Pre-clinical work
  - MFMU
  - OPRU
  - FDA IND
  - OPRU Pilot phase 1
  - OPRC Phase 2
  - MFMU Phase 3
OPRU – Other Studies

- Glyburide and 17 OHP biotransormation
- Diclectin
- Opportunistic study
- Oseltamivir
- Glyburide and Metformin for GDM
- PD impact of vaginal and IM progestin on cervix
NICHD-OPRC
Current Sites

- University of Texas Medical Branch, Galveston, TX
  - Pravastatin to prevent preeclampsia
- Northwestern University, Chicago, IL
  - SSRI
- University of Pittsburg, Pittsburg, PA
  - Bupronorphine
- DM-Stat, Boston, MA
Challenges in conducting medications trials in pregnancy

- Patient enrollment
- Unlikely to consent when healthy
- Physiologic adaptations of pregnancy
- Perceived risk to pregnant women and fetuses/infants
- Pharmaceutical companies interest

Cohen-Wolkowiez M. obstet gynecol 2014
Possible Solutions

- Sampling strategies
- PK/PD modeling and simulation
- Increasing the support of PK trials in pregnancy
  - Private/government-funded organizations
  - Support existing networks charged to perform obstetric-fetal pharmacology studies
  - Incentivize pharmaceutical companies
  - Obstetric pharmacology training programs
- Legislation

Cohen-Wolkowiez M. 2014
UTMB
Gary Hankins, MD
Mahmoud Ahmed, PhD
George Saade, MD
Tatiana Nanovskaya, PhD
Shannon Clark, MD
Wayne Snodgrass, MD, PhD
Sherif Abdel-Rahman, PhD
Erik Rytting, PhD

Perinatal Research Division
Holly West, ANP
Ashley Salazar, RN

Eunice Kennedy Shriver – NICHD
Anne Zajicek, MD, PharmD, FAAP
Zhaoxia Ren, MD, PhD

DM STAT
Kim Dukes, PhD
Julie Peterson

University of Pittsburg
Steve Caritis, MD
Raman Venkataramanan, PhD

Northwestern University
Katherine Wisner, MD
Catherine Stika, MD
Al George, MD
William Grobman, MD
Indiana University
David Flockhart, MD, PhD
David Hass, MD, MS
Laura Haneline, MD
Sara Quinney, PharmD, PhD

University Of Washington
Thomas Easterling, MD
Mary Hebert, PhD

Columbia University
Kirsten Cleary, MD
Mary D’Alton, MD

RTI
Linda Brown, PhD
Katrina Burson, RN

Eunice Kennedy Shriver – NICHD U10HD047891, U10HD063094,
U10HD047892, U10HD047905, and U10HD057753
Thank You
Fig. 3. Simplified view of the pharmacokinetics of pravastatin in humans.

Modified from Hatanaka T. Clin Pharmacokinet 2000

T Easterling, MD
Pravastatin Pharmacokinetics summary

- **Elimination**: Active transport
- **Portal flow**: ↓10% AUC - β blocker
- **CYP metabolism**: minor - oxidized metabolites
  - 1000-fold < other statins
- **P-glycoprotein**:
  - CNS - substrate (undetectable in brain)
- **Grapefruit juice**: no interaction
- **Cyclosporin**:
  - heart transplant 20-fold increase in AUC
  - renal transplant - several-fold higher

**MW 446**
**β-hydroxy acid**
**Hydrophilic**
**Protein binding**: (43-54%)
**High extraction ratio**
**Hepatoselective**
**Organic anion transporter**
**Biliary secretion**: (23% fecal)
**Renal tubular secretion**: (47%)
Project Development Timeline - Pravastatin

Pre-clinical experimental work

- Concept
- Protocol committee

Placental studies

- IND

Phase I
- FDA
- OPRU

Phase 2/3
- OPRU
- OPRC/MFMU

MFMU

OPRU

NCT01717586